

# Impaired left ventricular diastolic filling in patients with familial amyloid polyneuropathy: a pulsed Doppler echocardiographic study

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**SUMMARY** To assess left ventricular diastolic filling in patients with amyloid heart disease 12 patients with familial amyloid polyneuropathy and 15 normal subjects were studied by pulsed Doppler echocardiography. None of the patients had clinical evidence of overt heart disease or restrictive cardiomyopathy and only two of them showed ventricular wall thickening. The peak flow velocity of rapid diastolic filling and the acceleration rate of early diastolic inflow were significantly lower in patients with familial amyloid polyneuropathy than in controls. The pressure half time was significantly longer in patients than in controls. In addition, the peak flow velocity during atrial contraction and the ratio of atrial peak flow velocity to rapid diastolic peak flow velocity were significantly greater in patients than in controls. Although there were no significant correlations between measurements of diastolic filling and clinical findings in patients with familial amyloid polyneuropathy, the ratio of atrial peak flow velocity to rapid diastolic peak flow velocity was significantly related to left ventricular posterior wall thickness.

These findings suggest that in patients with cardiac amyloidosis without restrictive cardiomyopathy, abnormal left ventricular diastolic filling, manifested by a reduction in the rate and volume of rapid diastolic filling with enhanced atrial contraction, can be seen even in the early stage of the disease.

Familial amyloid polyneuropathy causes progressive systemic amyloidosis with polyneuropathy that can affect the heart. Amyloid deposits have been reported in the myocardium when there is no clinically identifiable heart disease or ventricular wall thickening.<sup>1</sup> In earlier serial echocardiographic studies<sup>1,2</sup> we found that the development of extensive amyloid deposition caused not only progressive increases in ventricular wall thickness but also altered left ventricular systolic and diastolic function. Left ventricular diastolic filling in several cardiac diseases has been non-invasively assessed by pulsed Doppler echocardiography. But so far the profile of left

ventricular diastolic filling in patients with amyloid heart disease has not been precisely established by this technique.<sup>3-5</sup>

We have assessed left ventricular diastolic filling in patients with familial amyloid polyneuropathy who had no clinical evidence of overt heart disease.

## Patients and methods

### PATIENTS

We studied 12 patients with familial amyloid polyneuropathy (seven men and five women, aged 28 to 59 years; mean (SD) 42 (9)) and 15 healthy controls (10 men and five women, aged 27 to 58 years; mean (SD) 40 (10)). All patients were referred to us from several locations in Nagano Prefecture in the central part of Japan<sup>6</sup> and the diagnosis was based on neurological findings and amyloid deposits in biopsy

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specimens of the stomach, rectum, or sural nerve. None had clinically overt heart disease or restrictive cardiomyopathy or any known concomitant heart disease. The duration of illness ranged from 1.5 to 11 years (mean (SD) 6.2 (3.0)). Biopsy specimens of the right ventricular endomyocardium were taken from eight of the 12 patients and all of them showed histological evidence of amyloid deposition. Each subject gave informed consent at the time of the study.

#### M MODE AND PULSED DOPPLER ECHOCARDIOGRAPHIC EXAMINATIONS

Cross sectionally guided M mode and pulsed Doppler echocardiograms were obtained with a commercially available cross sectional Doppler echocardiograph (Toshiba, model SSH-40A/SDS-21A), with a 2.4 MHz transducer, at paper speeds of 50 to 100 mm/s. All subjects were examined in the left lateral recumbent position and were in sinus rhythm with heart rate of 62 to 74 beats/min at the time of the study.

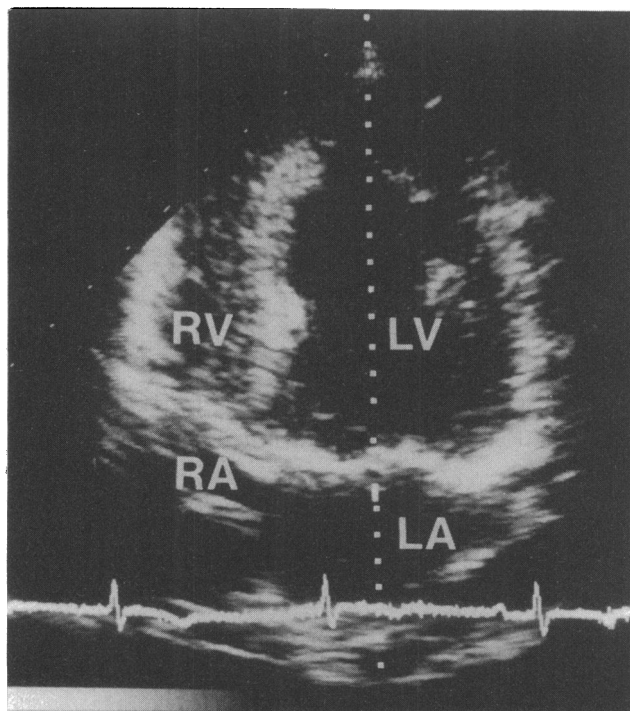
In the M mode echocardiographic examination, the following variables were measured according to the criteria recommended by the American Society of Echocardiography<sup>7</sup>: (a) left ventricular end diastolic and end systolic dimension and (b) left ventricular

posterior wall thickness at end diastole. All measurements were made in at least three cardiac cycles and averaged with the aid of a computer interfaced graphic analyser (Kontron, model Cardio-200). Then fractional shortening was calculated.

Doppler recordings of transmitral flow velocity were taken through an apical four chamber view with the Doppler cursor oriented parallel to the long axis plane of the left ventricle and the sample volume carefully placed at the level of the mitral annulus (fig 1). The following measurements were obtained (fig 2): (a) peak flow velocity of left ventricular rapid diastolic filling (peak E), (b) peak flow velocity during atrial contraction (peak A), (c) the ratio of peak A to peak E, (d) acceleration rate of left ventricular early diastolic flow, (e) acceleration time of early diastolic flow, and (f) pressure half time, which is defined as the time from peak E to peak E/ $\sqrt{2}$ .<sup>8</sup>

#### STATISTICAL ANALYSIS

Data are expressed as mean (SD) and were analysed by an unpaired *t* test. Correlations between measurements derived from Doppler echocardiography and clinical and M mode echocardiographic findings were assessed by linear regression analysis. Statistical significance was assumed when the *p* value was < 0.05.



**Fig 1** Stop frame cross sectional echocardiogram in the apical four chamber view showing the typical position of the pulsed Doppler sample volume used to obtain left ventricular diastolic flow-velocity waveforms. The sample volume is positioned just below the mitral valve annulus. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

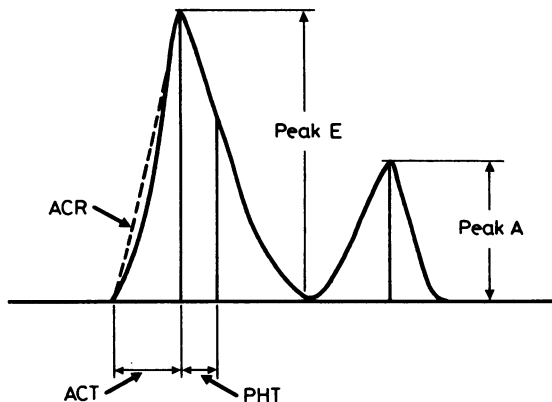


Fig 2 Measurement of the left ventricular inflow pattern. ACR, acceleration rate of left ventricular early diastolic flow; ACT, acceleration time of left ventricular early diastolic flow; PHT, pressure half time; peak A, peak flow velocity during atrial contraction; peak E, peak flow velocity of left ventricular rapid diastolic filling.

## Results

### M MODE ECHOCARDIOGRAPHIC FINDINGS

Table 1 shows that the age and sex distribution, heart rate, left ventricular cavity size, and fractional shortening were similar in patients with familial amyloid polyneuropathy and in controls. Although 10 (83%) of the 12 patients had normal left ventricular posterior wall thickness, this was slightly but significantly greater in patients than in controls.

### PULSED DOPPLER ECHOCARDIOGRAPHIC FINDINGS

The peak E during rapid diastolic filling and the acceleration rate of early diastolic flow in patients with familial amyloid polyneuropathy were 39 (9) cm/s and 352 (73) cm/s<sup>2</sup>, compared with 51 (11) cm/s ( $p < 0.01$ ) and 514 (130) cm/s<sup>2</sup> ( $p < 0.001$ ) in controls, respectively. The pressure half time was

Table 1 Clinical characteristics of patients with familial amyloid polyneuropathy (FAP)

	FAP	Controls	p value
Number	12	15	
Age (mean (SD))	42 (9)	40 (10)	NS
Male/female	7/5	10/5	
Duration of illness (yr)	6.2 (3.0)		
HR (beats/min)	64 (4)	66 (4)	NS
EDD (mm)	46 (4)	48 (4)	NS
ESD (mm)	31 (6)	32 (4)	NS
PWT (mm)	9.6 (2.9)	8.3 (0.6)	< 0.05
%FS (%)	36 (5)	38 (4)	NS

EDD, end diastolic diameter; ESD, end systolic diameter; %FS, percentage fractional shortening; HR, heart rate; PWT, left ventricular posterior wall thickness.

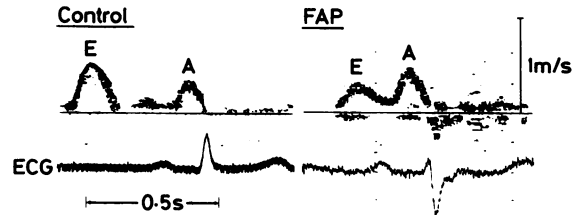


Fig 3 Pulsed Doppler waveform of left ventricular diastolic flow velocity. Left panel, from a 41 year old control with peak flow velocity of left ventricular rapid diastolic filling (E) higher than peak flow velocity during atrial contraction (A). Right panel, from a 38 year old patient with familial amyloid polyneuropathy (FAP) with A higher than E. ECG, electrocardiogram.

significantly longer in patients than in controls (70 (8) v 52 (10) ms,  $p < 0.001$ ). The peak A during atrial contraction and the ratio of peak A to peak E were significantly greater in patients than in controls (42 (6) v 30 (7) cm/s,  $p < 0.001$  and 1.14 (0.28) v 0.62 (0.19),  $p < 0.001$ , respectively) (fig 3 and table 2). Of the 10 patients without ventricular wall thickening, nine showed abnormal left ventricular diastolic filling. These included reduced peak E in seven patients, decrease in the acceleration rate of early diastolic flow in five, prolonged pressure half time in nine, enhanced peak A in seven, and increased ratio of peak A to peak E in eight.

Although there were no significant correlations between measurements of left ventricular diastolic filling and heart rate, left ventricular cavity size, or fractional shortening, the ratio of peak A to peak E was significantly related to left ventricular posterior wall thickness ( $r = -0.66$ ,  $p < 0.05$ ). In addition, no measurement correlated significantly with age and duration of illness, though the frequency and magnitude of abnormalities in peak E, peak A, and the ratio of peak A to peak E tended to increase with age and duration of illness (figs 4 and 5).

## Discussion

Our results show that in patients with familial amyloid polyneuropathy an abnormal pattern of left ventricular diastolic filling is detected by transmitral

Table 2 Mean (SD) Doppler flow measurements

Measurement	FAP	Controls	p value
Peak E (cm/s)	39 (9)	51 (11)	< 0.01
Peak A (cm/s)	42 (6)	30 (7)	< 0.001
Peak A/Peak E	1.14 (0.28)	0.62 (0.19)	< 0.001
ACR (cm/s <sup>2</sup> )	352 (73)	514 (130)	< 0.001
ACT (ms)	108 (19)	104 (25)	NS
PHT (ms)	70 (8)	52 (10)	< 0.001

See fig 2 for abbreviations.

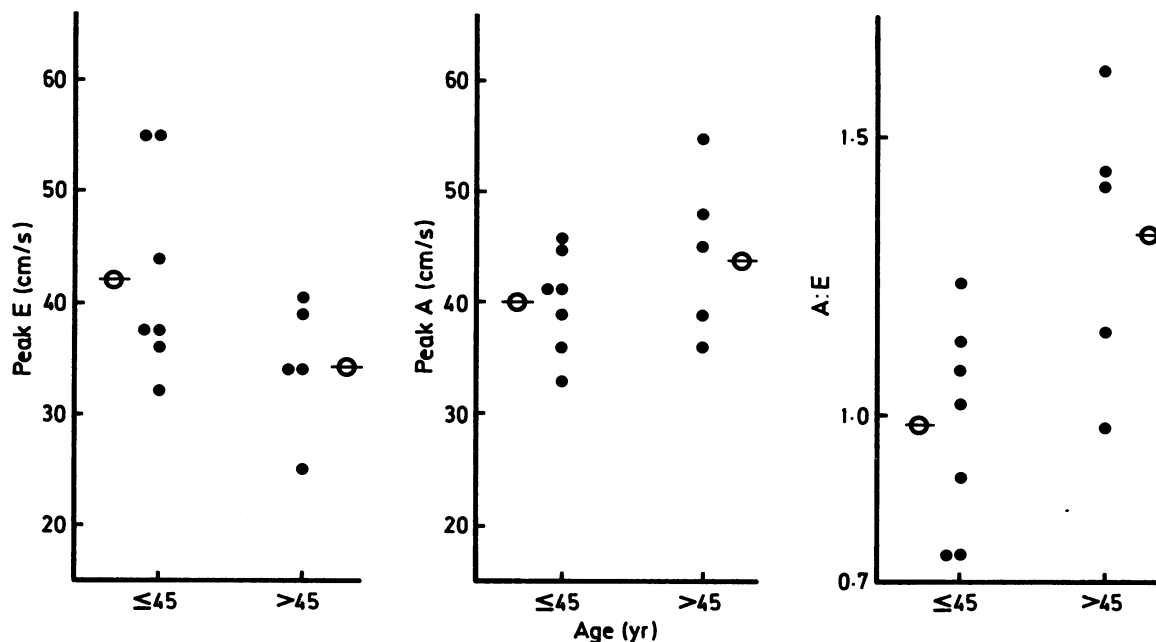


Fig 4 Comparison of measurements of left ventricular filling between patients with familial amyloid polyneuropathy aged  $\leq 45$  and  $> 45$  (peak flow velocity of left ventricular rapid diastolic filling (peak E), peak flow velocity during atrial contraction (peak A), and the ratio of peak A to peak E (A:E)). Mean values are also given.

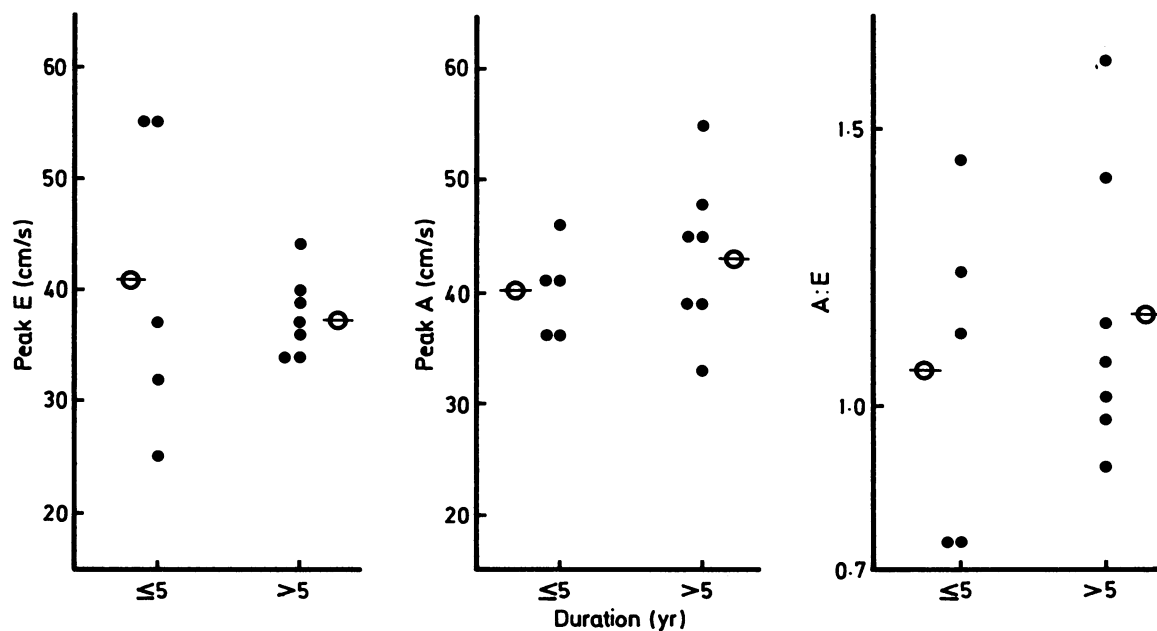


Fig 5 Comparison of measurements of left ventricular filling between patients with familial amyloid polyneuropathy who had been ill for less than five years and those ill for more than five years (peak E measurements, peak A measurements, and ratio of peak A to peak E (A:E) measurements). Mean values are also given.

flow velocity and that this can be identified even in the absence of clinically overt heart disease, ventricular wall thickening, and abnormal systolic function. Our results also show that abnormalities in diastolic filling increase with age and the duration of illness in patients with familial amyloid polyneuropathy.

#### LEFT VENTRICULAR DIASTOLIC FILLING IN PATIENTS WITH AMYLOID HEART DISEASE

Numerous invasive and non-invasive studies have shown that left ventricular diastolic filling is invariably impaired in patients with amyloid heart disease. Catheter studies showed an accelerated rapid diastolic filling followed by a cessation of filling in mid to late diastole in patients with amyloid restrictive cardiomyopathy.<sup>9,10</sup> But uniformly depressed filling was reported in some patients in the absence of a dip and plateau pattern in left ventricular pressure recordings.<sup>10,11</sup> Recently St John Sutton *et al* used digitised M mode echocardiography to show a prolonged isovolumic relaxation time and reduced peak filling rate of rapid diastolic filling in patients with primary and myeloma associated amyloidosis.<sup>12</sup> More recently, a range of abnormalities in left ventricular diastolic filling has been reported in patients with amyloid heart disease studied by pulsed Doppler echocardiography. In patients without obvious echocardiographic evidence of myocardial involvement, impaired relaxation of the left ventricle was manifested by a decrease in the rate and volume, as well as a prolongation of rapid filling and enhanced atrial systolic filling.<sup>4,5</sup> On the other hand, in patients with increased chamber stiffness with resultant restriction of diastolic filling, rapid filling rate was increased and was accompanied by normal or reduced atrial systolic filling of the left ventricle.<sup>3,5</sup> Thus both types of abnormal diastolic filling seem to be present to variable degrees in patients with amyloid heart disease.

In our study an abnormal pattern of left ventricular diastolic filling was detected in many patients with familial amyloid polyneuropathy and was characterised by a reduction in the rate and volume as well as a prolongation of rapid diastolic filling with exaggerated atrial systolic filling. In most of our patients amyloid heart disease was in the early stages<sup>1,2</sup>; none of them showed clinically overt heart disease, restrictive cardiomyopathy, or abnormal fractional shortening and most had normal ventricular wall thickness. Our Doppler findings were consistent with those of Plehn *et al*<sup>4</sup> and Klein *et al*,<sup>5</sup> in which patients had no evidence or slight echocardiographic evidence of myocardial involvement. Our results also confirmed that abnormal left ventricular diastolic filling can be seen before the

development of clinically overt heart disease, left ventricular wall hypertrophy, or abnormal systolic function.<sup>1,13</sup>

In our study only the ratio of peak A to peak E correlated significantly with the thickness of the left ventricular posterior wall, while individual peak velocities or other clinical findings did not. Although the flow direction at the centre of the mitral orifice might be assumed to be perpendicular to the mitral annulus, it was difficult to be certain that the apical view showed the true alignment of the mitral annulus. This might explain why only the ratio of peak A to peak E, which eliminated this factor, correlated with the wall thickness. In patients with amyloid heart disease, ventricular wall hypertrophy has generally been reported to be caused by amyloid infiltration into the myocardium as well as resultant fibrosis.<sup>14,15</sup> We did not measure the extent of amyloid infiltration or fibrosis in any of our patients.

We believe that the mechanism for abnormal diastolic filling in this disorder is likely to be abnormal left ventricular distensibility related to interstitial accumulation of amyloid and collagen. Furthermore, myocardial ischaemia may also lead to abnormalities in diastolic filling; several necropsy studies showed amyloid deposits in the intramural coronary arteries in patients with cardiac amyloidosis.<sup>14,16-18</sup>

#### CLINICAL IMPLICATIONS

We found age related changes in peak E, peak A, and the ratio of peak A to peak E in patients with familial amyloid polyneuropathy. Moreover, abnormalities in these measurements increased with the duration of illness. So these factors must be considered when assessing diastolic events in patients with familial amyloid polyneuropathy.

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